

## REMARKS

### Claim Amendments

Claims 34-38 and 43-51 are pending in the application. Claim 34 is amended and new claims 43-51 are added. The amendments are fully supported by the specification as filed. In particular, basis for the amended claim 34 and newly added claims 43-51 can be found in the originally filed claims including, for example, claims 6-13 and 23-27 of the application as filed. Therefore, the amendments do not introduce new matter.

### Supplemental IDS

Concurrently submitted herewith are two references, Presta et al. (1997) *Cancer Research* 57:4593-4599 and Chen et al. (1999) *J. Mol. Biol.* 293:865-881. Both references are published after the filing date of the present application, but may be helpful for further clarifying the claimed subject matter and many working examples of the present application. The Chen et al. reference is discussed below in regard to the rejections under 35 U.S.C. §§ 102 (a) and (f).

### Rejections Under 35 U.S.C. §§ 102 (a) and (f)

Claims 34-38 are rejected under 35 U.S.C. §§ 102 (a) and (f). The Examiner acknowledges applicants' Katz declaration by Dr. Leonard Presta submitted May 23, 2002, in regard to the previous 102(a) rejection over Baca et al. (1997) *JBC* 272:10678-10684 ("Baca et al."). But the Examiner notes that two of the inventors of the present invention, Henry Lowman and Yvonne Chen, are not listed as authors of the Baca et al. reference, and therefore it is an ambiguity to the Examiner as to the contribution of these inventors to the present invention. The Examiner further requests applicants to provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone, including Henry Lowman and Yvonne Chen are inventors of the claimed invention.

In response to the Examiner's rejections and inquires, applicants submit that the current invention resulted from a series of experiments employing different approaches for humanizing anti-VEGF antibodies. In the Amendment submitted on September 7, 2001 (Paper #30), applicants explained in detail the teachings provided in Examples 1-3 of the specification (pages 4-6 of Paper #30). Applicants note that the Baca et al. reference describes the methods and results that are substantially the same as that disclosed in Example 2 of the current specification (pages 59-67). Briefly, it relates to humanizing a murine anti-VEGF antibody by randomizing a small set of framework residues and by monovalent

display of the resultant library of antibody molecules on the surface of filamentous phage in order to identify high affinity framework sequences via affinity-based selection.

Applicants further submit herewith a reference entitled "Selection and Analysis of an Optimized Anti-VEGF Antibody: Crystal Structure of an Affinity-matured Fab in Complex with Antigen" by Chen et al. (1999) *J. Mol. Biol.* 293(4):865-881. The Chen et al. reference describes affinity-maturation of humanized anti-VEGF antibodies through CDR mutation followed by affinity selection using monovalent phage display, which is substantially similar to the disclosure in Example 3 of the present specification. Both Henry Lowman and Yvonne Chen are co-authors of the reference.

During a telephone discussion with the Examiner on November 5, 2002, applicants' representative explained the working examples of the specification and their correlation to the above-mentioned references. The Examiner indicated that such explanations along with submission of the subject reference would be sufficient to overcome the rejections.

Therefore, applicants have provided sufficient evidences and explanations as to the subject invention and contribution by the inventors. Accordingly, the rejections under 35 U.S.C. §§ 102 (a) and (f) are respectfully requested to be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 34-38 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ferrara et al. WO 94/10202 ("Ferrara et al"), and further in view of Adair et al. WO91/09967 ("Adair et al") and Yelton et al. (1995) *J. Immun.* 155:1994-2004 ("Yelton et al").

The Examiner maintains that it would have been prima facie obvious to humanize the anti-VEGF antibody of Ferrara et al by the methods of Adair et al and Yelton et al., and that the antibody so produced would have the binding and inhibition characteristics as previously recited in claim 34.

Applicants respectfully disagree with the Examiner's position, and maintain that one of ordinary skill in the art, applying the general methods of Adair et al or Yelton et al to the anti-VEGF antibody of Ferrara et al, would not have had reasonable expectation of success in producing a humanized anti-VEGF antibody having both the binding affinity and the inhibition potencies as previously claimed. However, in the interest of expediting the prosecution process, claim 34 has been amended to recite certain structural characteristics of the encoded humanized variant of a parent anti-VEGF antibody. Specifically, the CDRs of the heavy chain have defined amino acid sequences. Similarly, new claims 43-51 also incorporate various sequence characteristics for the encoded humanized variants. Applicants submit that these structural characteristics of the claimed subject matter further distinguish the present invention from that

described or suggested in the cited references. Accordingly, the claims as amended are patentable and the rejection under 35 U.S.C. §103(a) is respectfully requested to be withdrawn.

### SUMMARY

Applicants thank the Examiner for his consideration of proposed claim amendments and his many useful comments regarding the subject application during a telephone interview with Applicants' representative on January 10, 2003. Claim 34 has been further amended at the Examiner's suggestion.

Claims 34-38 and new claims 43-51 are pending in the application.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

GENENTECH, INC.

Date: August 15, 2003

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